

Amendments to the Specifications

Please replace paragraph [0165] with the following paragraph:

EXAMPLE 3

Particle Size, Particle Density, and Rate of Inhalable Particle Formation of Buprenorphine Aerosol

[0165] A solution of 1.5 mg buprenorphine in 100 μL 50/50 mixture of dichloromethane and methyl ethyl ketone was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The dichloromethane and methyl ethyl ketone mixture were allowed to evaporate. Assuming a drug density of about 1g/cc, the calculated thickness of the buprenorphine coating on the 24.5 cm² aluminum solid support, after solvent evaporation, is about 0.6 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were left open and the third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 6 s. The aerosol was analyzed by connecting the 1 L flask to an eight-stage Andersen non-viable cascade impactor. Results are shown in table 1. MMAD of the collected aerosol was 1.1 microns with a geometric standard deviation of 4.2. Also shown in table 1 is the number of particles collected on the various stages of the cascade impactor, given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle, $\pi D^3/6$, multiplied by the density of the drug (taken to be 1 g/cm³). The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L, giving an inhalable aerosol particle density of 7.2×10^7 particles/mL. The rate of inhalable aerosol particle formation is the sum of the numbers of particles collected on impactor stages 3 through 8 divided by the formation time of 6 s, giving a rate of inhalable aerosol particle formation of 1.2×10^{10} particles/second.

Table 1: Determination of the characteristics of a buprenorphine condensation aerosol by cascade impaction using an Andersen 8-stage non-viable cascade impactor run at 1 cubic foot per minute air flow.

Stage	Particle size range (microns)	Average particle size (microns)	Mass collected (mg)	Number of particles
0	9.0-10.0	9.5	0.01	3.1×10^4
1	5.8-9.0	7.4	0.02	1.1×10^5

2	4.7-5.8	5.25	0.03	4.1×10^5
3	3.3-4.7	4.0	0.05	1.5×10^6
4	2.1-3.3	2.7	0.10	9.7×10^6
5	1.1-2.1	1.6	0.19	8.9×10^7
6	0.7-1.1	0.9	0.08	2.1×10^8
7	0.4-0.7	0.55	0.03	3.4×10^8
8	0-0.4	0.2	0.30	7.2×10^{10}

Please replace paragraph [0166] with the following paragraph:

EXAMPLE 4

Drug Mass Density and Rate of Drug Aerosol Formation of Buprenorphine Aerosol

[0166] A solution of 1.2 mg buprenorphine in 100 μ L 50/50 mixture of dichloromethane and methyl ethyl ketone was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The dichloromethane and methyl ethyl ketone were allowed to evaporate. Assuming a drug density of about 1g/cc, the calculated thickness of the buprenorphine coating on the 24.5 cm² aluminum solid support, after solvent evaporation, is about 0.5 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were left open and the third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within seconds, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with formation of the aerosol terminated after 6 s. The aerosol was allowed to sediment onto the walls of the 1 L flask for approximately 30 minutes. The flask was then extracted with acetonitrile and the extract analyzed by HPLC with detection by light absorption at 225 nm. Comparison with standards containing known amounts of buprenorphine revealed that 0.2 mg of > 99% pure buprenorphine had been collected in the flask, resulting in an aerosol drug mass density of 0.2 mg/L. The aluminum foil upon which the buprenorphine had previously been coated was weighed following the experiment. Of the 1.2 mg originally coated on the aluminum, 0.7 mg of the material was found to have aerosolized in the 6 s time period, implying a rate of drug aerosol formation of 0.1 mg/s.